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Toxicokinetics of toluene in occupationally exposed volunteers

by Maria Wallén, MSc¹

WALLÉN M. Toxicokinetics of toluene in occupationally exposed volunteers. *Scand J Work Environ Health* 12 (1986) 588—593. The influence on the kinetics of toluene from long-term occupational exposure, cigarette smoking, and ethanol consumption was studied in 26 male spray painters. A group of spray painters with reported subjective symptoms such as concentration deficits, fatigue, and dizziness due to the solvent exposure did not differ in the uptake and disposition of toluene from a group of spray painters with no symptoms. In occupationally exposed workers, a tendency for an enhanced clearance of toluene from the blood was observed in relation to personal habits such as smoking and/or moderate chronic ethanol intake. Long-term occupational exposure to a mixture of organic solvents does not exert any effect on the metabolic rate of toluene as compared with that of an unexposed group.

Key terms: cigarette smoking, experimental exposure, kinetics, personal habits, spray painters, susceptibility to solvent exposure.

It is common knowledge that differences between people do exist, including their responsiveness to drugs. Among factors known to contribute to the variability in drug response are diseases, genetic factors, intake of other drugs, ethanol, dietary habits, pollutants, cigarette smoking, age, body composition, and sex (22). From studies on rats and on humans it is well known that drug metabolism is inhibited by acute ethanol intoxication (23) and enhanced after chronic ethanol intake (16). Furthermore, drugs, as well as ethanol, have been shown to affect the metabolism of aromatic organic solvents in man (4, 21, 37, 40, 43).

The toxicokinetics of industrially used organic solvents in man have been focused upon in several laboratory exposure experiments (2, 3, 4, 7, 20, 26, 34, 37, 38, 40, 41). However, most of these studies were carried out with young healthy volunteers with no history of occupational exposure to solvents or other agents that could affect the kinetics of the solvent studied.

In light of these facts it was considered pertinent to carry out a toxicokinetic study on volunteers with long-term occupational exposure to organic solvents. Toluene was considered the most suitable solvent to use in the present study. The advantages of using toluene are several. It is one of the most frequently used organic solvents in Swedish industry. It has a well-documented metabolic pathway, namely, microsomal hydroxylation by cytochrome p-450 and further oxidation through alcohol and aldehyde to the corresponding

acid (11, 42). The toxicokinetics of toluene in volunteers that have not been exposed earlier are also known (2, 26, 34, 35, 36, 38, 40).

The aim of this investigation was to show experimentally the effects on the toxicokinetics of toluene from long-term occupational exposure. Special attention was paid to workers with reported subjective susceptibility to solvent exposure and to cigarette smoking. The toxicokinetic approach to this problem gives the opportunity to study absorption and disposition from a well-defined dose of toluene and also the kinetics of these processes under the influence of other agents. The results are discussed in relation to toxicity.

The following three hypotheses were formulated:

1. The variability between workers in the susceptibility to toluene due to daily solvent exposure may be detected in the toxicokinetic parameters. In a test of this theory, the examined subjects were divided into two groups, one with and one without subjective symptoms such as autonomic symptoms, concentration deficits, fatigue, tiredness, and dizziness from the solvent exposure. The selection and grouping of the subjects have been described elsewhere (13).
2. Cigarette smoking, known to affect drugs extensively metabolized by the hepatic microsomal enzymes, has an effect on the toxicokinetics of toluene. In the testing of this theory, the exposed subjects were divided into smokers and nonsmokers.
3. The toxicokinetics of toluene in subjects with long-term occupational exposure to solvents differ from that of volunteers that have not been exposed to solvents earlier. The kinetic parameters obtained in the painter group were therefore compared with those from a group of volunteers with no history of occupational exposure to organic solvents.

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Subjects and methods

Subjects

Twenty-six men (age 19–64 years, weight 63–125 kg, height 171–207 cm), all of them occupationally exposed to organic solvents, participated as volunteers in the experiment. They had been occupationally exposed to organic solvents for 1–35 years (figure 1). The subjects were employed as spray painters at many different small workshops where painting of repaired cars and new industrial products was performed. The chemical hazards of spray painters result from exposure to solvent, dust, and metals and have been thoroughly described by Elofsson et al (5). The total solvent exposure, calculated as the additive hygienic effect, was, in that study, estimated to be one-fourth of the Swedish occupational exposure limit. As the group of workers in the present study was selected from similar workshops as the exposed group in the study of Elofsson et al (5), the exposure conditions can be considered similar in both investigations.

The volunteers were chosen from a group of 153 spray painters who received a self-administered questionnaire selecting for reported subjective symptoms such as concentration deficits, fatigue, and dizziness from solvent exposure. Two extreme groups were thereafter formed — one with reported subjective symptoms ($N = 16$) and one without ($N = 16$) (13). The group was reduced by three persons, who were prevented from taking part in the investigation. A general medical examination, including present and previous state of health preceded the exposures and resulted in the omission of another three persons (two from ethanol abuse and one from allergy). None of the reasons for not participating in the study were related to solvent exposure. Individuals participating in the exposure experiment were considered healthy with no detrimental effects on the functions of the respiratory or circulatory systems, no regular drug consumption, and no ethanol abuse.

The toxicokinetics of toluene in occupationally exposed volunteers were compared with data from a previous study of volunteers that had not been exposed earlier (40).

Experimental design

The volunteers were exposed to toluene (analytical grade, Merck, Darmstadt, Federal Republic of Germany) at the Swedish threshold limit value of 3.25 mmol/m³. The exposures were performed in an exposure chamber (volume 12 m³, air change 10 times/h, inlet airflow 115 m³/h, outlet airflow 135 m³/h). Solvent was injected into the influent air stream by means of a high-performance liquid chromatographic pump (Gilson 302). The toluene and carbon dioxide concentrations in the chamber were continuously monitored by an infrared spectrophotometer (Miran 80, Foxboro) at 13.77 and 14.18 μm , respectively, with

Figure 1. Years of employment as a spray painter (exposure years) versus age.

3.658 μm as the reference wavelength. The spectrophotometer was equipped with a 20-m gas flow cuvette and controlled by a personal computer (Apple III). In addition, intermittent monitoring of the toluene concentration in the chamber was gas chromatographically performed (Antec 464 LP, flame ionization detector, 3 % SE 30 on Chromosorb GAW, temperature 120°C, nitrogen flow 25 ml/min). The same gas chromatographic equipment was used to analyze samples of expired air for calculating the uptake of the solvent and end-exhaled air. (See the following section.) The air in the chamber was sampled from the upper central section of the chamber. The chamber was at the desired concentration when the volunteers entered. The variation in the exposure did not exceed ± 3 %, expressed as standard deviation throughout the exposure. The exposures lasted for 4 h and were preceded by a standardized diet since 1700 the previous day and until the end of the exposure day. The volunteers were instructed not to drink any alcoholic beverages the night before the exposure day. During the exposures, the subjects were sedentary and exposed in pairs.

Sampling and analysis

The pulmonary ventilation per unit of time and the uptake of toluene, calculated as the difference between inhaled and exhaled amounts of solvent, was measured with the Douglas bag technique. The air volume was measured with a balanced spirometer. The total uptake during the whole exposure period was calculated from the mean amounts of toluene taken up during each of four 8-min sampling periods. The time intervals for the sampling, the two volunteers exposed simultaneously being measured separately, were 30–38 or 40–48, 66–74 or 76–84, 142–150 or 152–160, and 172–180 or 182–190 min, respectively, after the onset of the exposure. The error of the method was estimated at ± 3 % from a comparable study (41). The end-exhaled air was sampled four times (88, 140, 171, and 235 min after the onset of exposure) at the end of a normal exhalation. In the collection of end-exhaled air the subject was asked to take three normal

breaths through a glass tube (volume 35 ml) and to close it tightly at both ends immediately after the third exhalation. Stop cocks with teflon-lined rubber membranes were used. The samples were prewarmed to 37°C in a thermostat before the gas chromatographic analysis. The error of the method was $\pm 12\%$.

Toluene concentrations in the blood were determined at selected intervals during the exposure and for 3.0 h during the postexposure period. (See figure 2.) The toluene concentration in the blood was determined gas chromatographically from capillary blood (200 μ l) sampled from a prewarmed fingertip. The blood samples were temperature equilibrated for at least 30 min and analyzed within approximately 2 h after the sampling. The error of the method was $\pm 3.9\%$. For details of the analytical procedures, see reference 40.

Statistical treatments

The Wilcoxon's rank test for independent observations (the Mann-Whitney test) was used to determine the significance of the differences between the values. For comparisons of proportions in independent samples the chi-square test corrected for continuity or Fisher's exact test was used. The nonparametric rank correlation test of Spearman was used to evaluate the correlation of age and body weight to the toxicokinetic parameters. A probability of <0.05 was chosen as the level of significance. The results are, unless otherwise stated, presented as means and standard deviations. The calculation of the error of the method for a single determination was based on the differences between a series of double determinations and expressed as the percentage of the mean values. Statistical testings were performed as described by Snedecor (31).

Results

In the evaluation of the uptake and disposition of toluene, the following parameters were estimated: the pulmonary ventilation per time unit, blood: end-exhaled air concentration ratio, the relative uptake, the total uptake, the area under the blood concentration versus the time curve, and the apparent clearance from the blood. No differences between the groups with and without reported subjective symptoms could be seen for any of these parameters (table 1). The concentrations of toluene in blood during the exposure and 3 h postexposure are shown in figures 2a and 2b for the whole group and the subgroups, respectively.

When the examined group was divided into smokers and nonsmokers, a tendency for a more rapid apparent clearance of toluene from the blood was seen in the smoker group, 1.7 (SD 0.4) l/h $\cdot$ kg, as compared to the nonsmoker group, 1.4 (SD 0.4) l/h $\cdot$ kg (table 1). Although the difference was not statistically significant ($p > 0.05$ in the rank sum test), it was close to the limit of significance and indicated a tendency for an enhanced clearance. Indeed, when the groups with and without subjective symptoms were subdivided into smokers and nonsmokers, the same tendency was observed in each group (table 1). The concentrations of toluene in the blood versus time in the smoker and nonsmoker groups are shown in figure 2c.

The daily intake of ethanol among the volunteers was estimated (data from the general medical examination preceding the exposures), and the examined group was divided into two parts on the basis of the amount of consumed ethanol (table 2). When the smoking habits and ethanol consumption were compared, it was found that the nonsmokers had a slightly smaller intake of ethanol than the smokers [$X^2 =$

Table 1. Age, weight, pulmonary ventilation ($\dot{V}_E$), blood: end-exhaled air concentration ratio, relative uptake (F),^a total uptake (U_t),^b integrated dose (AUC),^c and the apparent clearance ($CL_{b(app)}$).^d

	Age (years)			Weight (kg)			$\dot{V}_E$ (l/min)			Blood: air concentration ratio			F (%)			U_t (mmol)			AUC (mmol $\cdot$ h/l)			$CL_{b(app)}$ (l/h $\cdot$ kg)		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
<i>Group with symptoms</i>																								
Smokers	10	33.4	8.2	10	77.3	15.0	7	11.2	2.0	10	7.0	1.5	10	56.8	4.8	7	4.7	0.8	10	0.035	0.015	7	1.7	0.5
Nonsmokers	4	43.0	14.2	4	82.9	8.7	3	10.2	0.9	4	7.2	1.2	4	55.8	1.7	3	4.1	0.5	4	0.034	0.006	3	1.5	0.3
Entire group	14	36.1	10.7	14	78.9	13.4	10	10.9	1.8	14	7.1	1.4	14	56.5	4.1	10	4.5	0.8	14	0.035	0.013	10	1.6	0.4
<i>Group without symptoms</i>																								
Smokers	5	34.4	8.8	5	78.4	10.1	5	9.9	0.8	5	6.8	2.3	5	56.8	2.0	5	4.0	0.4	5	0.031	0.004	5	1.7	0.3
Nonsmokers	7	35.5	14.7	7	86.3	18.0	6	10.3	1.7	7	6.5	1.5	7	57.6	3.7	6	4.0	1.2	7	0.032	0.012	6	1.4	0.4
Entire group	12	34.7	12.1	12	83.0	15.2	11	10.2	1.3	12	6.6	1.8	12	56.5	3.3	11	4.0	0.9	12	0.032	0.009	11	1.5	0.4
<i>Both groups combined</i>																								
Smokers	15	33.7	8.1	15	77.7	13.2	12	10.7	1.7	15	7.0	1.7	15	57.1	4.1	12	4.4	0.7	15	0.034	0.012	12	1.7	0.4
Nonsmokers	11	37.9	14.4	11	85.1	14.8	9	10.3	1.4	11	6.9	1.4	11	56.5	3.0	9	4.0	1.0	11	0.033	0.010	9	1.4	0.4
Entire group	26	35.5	11.7	26	80.8	14.1	21	10.5	1.5	26	6.9	1.6	26	56.8	3.7	21	4.2	0.8	26	0.033	0.011	21	1.6	0.4

^a F (fraction absorbed per breath) = $(C_{in} - C_{ex}) \cdot 100 / C_{in}$, where C_{in} = the solvent concentration in inhaled air and C_{ex} = the solvent concentration in exhaled air.

^b $U_t = \dot{V}_E \cdot t \cdot (C_{in} - C_{ex})$, where t = duration of the exposure.

^c AUC, area under the blood concentration versus the time curve, was calculated by the trapezoidal rule during the exposure and for 3.0 h during the postexposure period. The remaining area was estimated from the equation $y = Ae^{-\alpha t} + Be^{-\beta t}$, where y is the solvent concentration in the blood, t represents the time, A and B are the y intercepts, and α and β are slopes of lines. β was determined, and the remaining area calculated as $C_{b(180 \text{ min postexposure})} / \beta$, where C_b equals the solvent concentration in the blood. The terminal phase was disregarded.

^d $CL_{b(app)} = U_t / AUC \cdot kg$. U_t , the total uptake, was regarded as the dose since small lipophilic molecules like toluene rapidly diffuse from the alveoli into the blood (1, 8).

^e N = number of subjects.

^f The parameters $\dot{V}_E$, U_t , and $CL_{b(app)}$ are missing for five subjects because of poor measurements of the pulmonary ventilation rate.

Figure 2. Blood concentrations of inhaled toluene (3.25 mmol/m^3) over a 4-h period. The end of the exposure is marked with an arrow. (a = all subjects (filled circles), b = group with reported subjective symptoms (unfilled stars) and group without reported subjective symptoms (filled stars), and c = smokers (unfilled triangles) and nonsmokers (filled triangles). The standard deviations in 2b and 2c are of the same magnitude as those shown in figure 2a.

5.6727 , $\alpha = 0.02$ ($N = 26$) and $\alpha = 0.05$ in Fisher's exact test ($N = 21$)). It was also found that the subjects with and without reported symptoms were randomly distributed between the groups (X^2 test and Fisher's exact test $\alpha > 0.05$).

The occupational exposure to organic solvents had no effect on the apparent clearance of toluene [$CL_{b(\text{app})} = 1.6 \pm 0.4 \text{ l/h} \cdot \text{kg}$ ($N = 21$)] as compared to that obtained for the not occupationally exposed volunteers [$CL_{b(\text{app})} = 1.8 \pm 0.2 \text{ l/h} \cdot \text{kg}$ ($N = 10$)] ($p > 0.05$ in the rank sum test corrected for continuity).

Neither age nor body weight correlated with the toxicokinetic parameters as tested by the nonparametric rank correlation test of Spearman [correlation coefficients (r) > 0.05 in all cases].

Table 2. Consumption of ethanol, reported subjective symptoms to the solvent exposure, and cigarette smoking.

Increasing intake of ethanol	Reported symptoms ^a	Cigarette smoker ^a
< 10 g ethanol/d	—	—
	+	—
	+	—
	—	—
	—	—
	+	+
	—	—
	—	—
	+	+
	+	+
> 10 g ethanol/d	—	+
	+	+
	+	+
	+	+
	+	+
	+	+
	+	+
	+	+
	+	—
	—	+

^a + = yes, — = no.

Discussion

In the present study, in which subjects occupationally exposed to organic solvents were experimentally exposed to toluene, it was found that the apparent clearance of toluene from the blood did not differ from that in a group of previously unexposed volunteers. Although the two groups originated from studies on two different occasions, 1983 (40) and 1985 (the present study), they were regarded as comparable for the following reasons. The exposures were performed in the same exposure chamber with approximately the same time schedules for sampling, the same laboratory staff performed the experiments, and the same analytical equipment, as well as analytical procedures, were used. Furthermore, in both studies the effects on performance during the exposures were assessed by a group of psychologists at the institute (13, 14). Only minor discrepancies between the groups could be noted, such as smaller ranges in the age and weight of the group that was not preexposed than those of the preexposed one. However, in reference to the lack of correlation between the pharmacokinetic parameters studied and age or weight, the difference in range was considered of no importance for the results.

The hypothesis that the group with the reported subjective symptoms due to solvent exposure differed from the group with no symptoms in the rates of uptake and elimination of toluene was rejected.

As toluene is predominantly hepatically metabolized, the status of the liver and its metabolizing capacity is of great importance. Alterations in the metabolic rate

of toluene might be due to impairments in the liver functions, as the chemical hazards of the painters to some extent consisted of liver-damaging agents such as chlorinated hydrocarbons (5), known as hepatotoxins. The findings of no effects on the metabolic capacity from the occupational exposure to solvents conform with recent investigations in which the authors claim normal serum activities of liver enzymes after chronic solvent exposure in man (15, 17, 32). The subjects in these studies, including the present one, were fully fit for work and had not asked for health care because of suspected solvent intoxication.

Changes in the metabolic rate of toluene due to effects on the microsomal enzymatic system have been reported from a number of studies on animals. Induction of the microsomal enzyme activity in rat has been shown by, eg, Toftgård (33), Elovaara (6), and Pyykö (19). Furthermore, interactions have also been reported between toluene and ethanol (27, 28, 39), drugs (11), and other aromatic hydrocarbons (10, 12, 18, 24, 25). However, these effects, found in rats, were obtained from short-term exposures in comparison with the exposure of spray painters. The exposure levels in the animal experiments were also higher than those occurring during spray painting (5, 9).

It should not be excluded that our results might be due to the "healthy worker effect," ie, that even the painters with reported subjective symptoms still remained too healthy to show any detectable changes in their metabolic rate of toluene. It should also be noted that factors that could counteract an enhancing influence on the metabolism of toluene can certainly not be excluded.

Splitting the examined group into smokers and non-smokers showed a tendency towards enhanced elimination of toluene from the blood of the smokers. Cigarette smoking tends to reduce the clinical and toxic effects of drugs if the induction of microsomal enzymes causes a more rapid elimination of the drug (22). It has also been found that pulmonary aryl hydroxycarbon hydroxylase activity is enhanced in a variety of laboratory mammals after the inhalation of cigarette smoke (30). This phenomenon is so far in agreement with our findings. However, the slight alteration in the apparent clearance of toluene from the blood might equally well depend upon ethanol consumption. It is then the chronic effects of ethanol consumption that may affect the metabolic rate of toluene, as any acute effects of ethanol on the results were excluded.

Another factor that may contribute to an altered metabolic rate is dietary habits. Sato & Nakajima (25) have described how restricted carbohydrate intake and food deprivation each enhanced the metabolism of toluene in rats with little or no increase in microsomal protein and cytochrome p-450 contents. Furthermore a restricted intake of carbohydrate potentiates the effect of ethanol ingestion (29). As there was no control over dietary habits until the day before the exposure, the obtained effects of toluene on metabolism

might have been due to cigarette smoking, ethanol consumption, and dietary factors, each one alone or in any combination.

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The study has been approved by the Ethical Committee at the Karolinska Institute, Stockholm, Sweden.

References

1. Åstrand I. Effect of physical exercise on uptake, distribution and elimination of vapors in man. In: Fiserova-Bergerova V, ed. Modeling of inhalation exposure to vapors: Uptake, distribution, and elimination. Volume II. CRC Press, Boca Raton, FL 1983, pp 107-130.
2. Carlsson A. Exposure to toluene: Uptake, distribution and elimination in man. *Scand J Work Environ Health* 8 (1982) 43-45.
3. David A, Flek J, Frantik E, Gut I, Sedivec V. Influence of phenobarbital on xylene metabolism in man and rats. *Int Arch Occup Environ Health* 44 (1979) 117-125.
4. Dössing M, Baelum J, Honoré Hansen S, Lundqvist GR. Effects of ethanol, cimetidine and propranolol on toluene metabolism in man. *Int Arch Occup Environ Health* 54 (1984) 309-315.
5. Elofsson SA, Gamberale F, Hindmarsh T, Iregren A, Isaksson A, Johnsson I, Knave B, Lydahl E, Mindus P, Persson HE, Philipson B, Steby M, Struwe G, Söderman E, Wennberg A, Widén L. Exposure to organic solvents: A cross-sectional epidemiologic investigation on occupationally exposed car and industrial spray painters with special reference to the nervous system. *Scand J Work Environ Health* 6 (1980) 239-273.
6. Elovaara E, Savolainen H, Pfäffli P, Vainio H. Effects of subacute toluene inhalation on its metabolism and disposition in rat. *Arch Toxicol* (1979): suppl 2, 345-348.
7. Engström K, Riihimäki V, Laine A. Urinary disposition of ethylbenzene and m-xylene in man following separate and combined exposure. *Int Arch Occup Environ Health* 54 (1984) 355-363.
8. Goldstein A, Aronow L, Kalman SM, ed. Principles of drug action: The basis of pharmacology. Wiley, New York, NY 1974, pp 129-225.
9. Hänninen H, Eskelinen L, Husman K, Nurminen M. Behavioral effects of long-term exposure to a mixture of organic solvents. *Scand J Work Environ Health* 2 (1976) 240-255.
10. Ikeda M. Reciprocal metabolic inhibition of toluene and trichloroethylene in vivo and in vitro. *Int Arch Arbeitsmed* 33 (1974) 125-130.
11. Ikeda M, Ohtsui H. Phenobarbital-induced protection against toxicity of toluene and benzene in the rat. *Toxicol Appl Pharmacol* 20 (1971) 30-43.

12. Ikeda M, Ohtsuiji H, Imamura T. In vivo suppression of benzene and styrene oxidation by co-administered toluene in rats and effects of phenobarbital. *Xenobiotica* 2 (1972) 101—106.
13. Iregren A. Subjective and objective signs of organic solvent toxicity among occupationally exposed workers: An experimental evaluation. *Scand J Work Environ Health* 12 (1986) 469—475.
14. Iregren A, Åkerstedt T, Anshelm Olson B, Gamberale F. Experimental exposure to toluene in combination with ethanol intake: Psychophysiological effects. *Scand J Work Environ Health* 12 (1986) 128—136.
15. Kurppa K, Husman K. Car painters' exposure to a mixture of organic solvents: Serum activities of liver enzymes. *Scand J Work Environ Health* 8 (1982) 137—140.
16. Lieber CS. Metabolism and metabolic effects of alcohol. *Semin Hematol* 17 (1980) 85—99.
17. Lundberg I, Håkansson M. Normal serum activities of liver enzymes in Swedish paint industry workers with heavy exposure to organic solvents. *Br J Ind Med* 42 (1985) 596—600.
18. Perbellini L, Leone R, Fracasso ME, Brugnone F, Venturini MS. Metabolic interaction between n-hexane and toluene in vivo and in vitro. *Int Arch Occup Environ Health* 50 (1982) 351—358.
19. Pykkö K. Effects of methylbenzenes on microsomal enzymes in rat liver, kidney and lung. *Biochim Biophys Acta* 633 (1980) 1—9.
20. Riihimäki V, Pfäffli P, Savolainen K, Pekari K. Kinetics of m-xylene in man: General features of absorption, distribution, biotransformation and excretion in repetitive inhalation exposure. *Scand J Work Environ Health* 5 (1979) 217—231.
21. Riihimäki V, Savolainen K, Pfäffli P, Pekari K, Sippel HW, Laine A. Metabolic interaction between m-xylene and ethanol. *Arch Toxicol* 49 (1982) 253—263.
22. Rowland M, Tozer TN, ed. *Clinical pharmacokinetics: Concepts and applications*. Lea & Febiger, Philadelphia, PA 1980.
23. Rubin E, Gang H, Misra PS, Lieber CS. Inhibition of drug metabolism by acute ethanol intoxication. *Am J Med* 49 (1970) 801—806.
24. Sato A, Nakajima T. Dose-dependent metabolic interaction between benzene and toluene in vivo and in vitro. *Toxicol Appl Pharmacol* 48 (1979) 249—256.
25. Sato A, Nakajima T. Enhanced metabolism of volatile hydrocarbons in rat liver following food deprivation, restricted carbohydrate intake, and administration of ethanol, phenobarbital, polychlorinated biphenyl and 3-methylcholanthrene: A comparative study. *Xenobiotica* 15 (1985) 67—75.
26. Sato A, Nakajima T, Fujiwara Y, Hirose K. Pharmacokinetics of benzene and toluene. *Int Arch Arbeitsmed* 33 (1974) 169—182.
27. Sato A, Nakajima T, Koyama Y. Effects of chronic ethanol consumption on hepatic metabolism of aromatic and chlorinated hydrocarbons in rats. *Br J Ind Med* 37 (1980) 382—386.
28. Sato A, Nakajima T, Koyama Y. Dose-related effects of a single dose of ethanol on the metabolism in rat liver of some aromatic and chlorinated hydrocarbons. *Toxicol Appl Pharmacol* 60 (1981) 8—15.
29. Sato A, Nakajima T, Koyama Y. Interaction between ethanol and carbohydrate on the metabolism in rat liver of aromatic and chlorinated hydrocarbons. *Toxicol Appl Pharmacol* 68 (1983) 242—249.
30. Smith BR, Bend JR. Metabolic interactions of hydrocarbons with mammalian lung. *Rev Biochem Toxicol* 3 (1981) 77—122.
31. Snedecor GW, Cochran WG, ed. *Statistical methods*. The Iowa State University Press, Ames, IA 1980.
32. Tähti H, Kärkkäinen S, Pykkö K, Rintala E, Kataja M, Vapaatalo H. Chronic occupational exposure to toluene. *Int Arch Occup Environ Health* 48 (1981) 61—69.
33. Toftgård R, Nilsen OG, Gustafsson JÅ. Dose-dependent induction of rat liver microsomal cytochrome p-450 and microsomal enzymic activities after inhalation of toluene and dichloromethane. *Acta Pharmacol Toxicol* 51 (1982) 108—114.
34. Veulemans H, Masschelein R. Experimental exposure to toluene: I Factors influencing the individual respiratory uptake and elimination. *Int Arch Occup Environ Health* 42 (1978) 91—103.
35. Veulemans H, Masschelein R. Experimental human exposure to toluene: II Toluene in venous blood during and after exposure. *Int Arch Occup Environ Health* 42 (1978) 105—107.
36. Veulemans H, Masschelein R. Experimental human exposure to toluene: III Urinary hippuric acid excretion as a measure of individual solvent uptake. *Int Arch Occup Environ Health* 43 (1979) 53—62.
37. Waldron HA, Cherry N, Johnston JD. The effects of ethanol on blood toluene concentrations. *Int Arch Occup Environ Health* 51 (1983) 365—369.
38. Wallén M, Holm S, Byfält Nordqvist M. Coexposure to toluene and p-xylene in man: Uptake and elimination. *Br J Ind Med* 42 (1985) 111—116.
39. Wallén M, Johanson G, Byfält Nordqvist M. The effects of ethanol on the kinetics of toluene in the perfused rat liver. *Toxicol Lett* 26 (1985) 59—64.
40. Wallén M, Näslund PH, Byfält Nordqvist M. The effects of ethanol on the kinetics of toluene in man. *Toxicol Appl Pharmacol* 76 (1984) 414—419.
41. Wigaeus E, Löf A, Bjurström R, Byfält Nordqvist M. Exposure to styrene: Uptake, distribution, metabolism and elimination in man. *Scand J Work Environ Health* 9 (1983) 479—488.
42. Williams RT, ed. *Detoxication mechanisms*. Wiley, New York, NY 1959, pp 194—196.
43. Wilson HK, Robertson SM, Waldron HA, Gompertz D. Effect of alcohol on the kinetics of mandelic acid excretion in volunteers exposed to styrene vapour. *Br J Ind Med* 40 (1983) 75—80.

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